REMARKS

Claim Amendments

Claim 30 is rewritten in independent form.

The independent claims (including the newly made independent claim 30) were amended to also recite that the administration is to a "to a patient in need thereof" and that administration is of "an effective amount of" the compounds of the claims. These amendments only further clarify the claims.

Claim 19 is amended to explicitly recite the definitions of n and n1 which were previously only defined in claim 17 from which it depended. This amendment does not change the scope of the claims, but merely further clarifies.

Claim 20 is amended to be dependent on claim 17. Previously it depended on claim 19, but it appears that the definitions for X and Z were broader therein than in claim 19. The amendment corrects this. Additionally, the definition of X and Z included Cl and F, which does not have basis in claim 17. The Cl and F atoms however can substitute the Q and Q^1 groups as the definition of B provides for such substitutions (see lines 5-6 of definition of B in claim 17). Thus, the amendments to claim 20 merely correct formality issues, but the scope of the claim is not changed.

Claim 26 is amended to be dependent on claim 30 since it had the same scope as claim 21 before the amendment.

Claim 17 is now directed to the treatment of "rheumatoid arthritis."

Support for the addition of Crohn's disease to claim 30, another disease mediated by p38, is found in the specification on page 2, line 25. Narrowing claim 17 to methods for treatment of rheumatoid arthritis necessited the expansion of the list of p38 mediated diseases in claim 30 to include Crohn's disease.

The definition of R^2 in all the claims now is "C_6-C_{14} aryl, or substituted C_6-C_{14} aryl."

No new issues are raised by the amendments that would prompt the requirement of further searching. The entry thereof is thus respectfully requested.

The Rejections Under 35 USC § 103

The claims are rejected as allegedly obvious over Creswell in combination with Adams. The methods claimed herein are clearly unobvious in that the combined teachings of these references do not suggest the synthesis of compounds of formula I and they do not suggest these compounds are effective in treating p38 mediated diseases.

Adams discloses only imadazole compounds and there is no mention these compounds include ureas. The teachings of Adam's add nothing to the teachings of Creswell to suggest synthesizing the pyrazole, furan and thiophene ureas claimed herein. In addition, the compounds disclosed by Adams and their function are so far removed from the teachings of Creswell that one skilled in the art would have no basis to assume the compounds of Creswell or those of similar structure, such as the compounds claimed herein, are effective in treating p38 mediated diseases, such as inflammatory diseases.

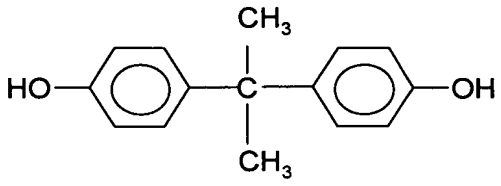
Creswell, which reference is relied on for the teaching of compounds, teaches compounds that do not overlap at all the compounds of the present claims. R^2 in the present independent claims is C_6-C_{14} aryl or substituted C_6-C_{14} aryl. The closest corresponding group on the compounds of Creswell disclosed generically, i.e., the R^{11} group on the group (8) in the definition of Het taught on column 3, line 26-31, is benzyl (which is a phenyl group bridged via a methylene group, which methylene bridge is not present in the claims), 2-pyridyl or hydrogen.

Even ignoring the lack of any overlap between the compounds of Creswell and of the present claims, one skilled in the art would not find it obvious to prepare pyrazole, furan or thiphene urea compounds of formula I herein with the bridged cyclic group for "B," i.e., one substituted with -Y-Ar. No bridged pyrazole compounds are described by Creswell. To obtain the bridged pyrazole compounds claimed herein it would be necessary to make the proper selection for at least four variables of Creswell, which are X, one of (R_1, R_2 and/or R_3), HET and R_{11}. Of these, no preference is given to values for R_1, R_2 and R_3 or R_{11} which would lead to the pyrazole compounds claimed herein. When considered as a whole, the teachings of Creswell, either alone or combined with Adams, provide no guidance as to the selection necessary to arrive at the pyrazole compounds claimed herein.

For obviousness to be present, there has to be more than a mere broad disclosure in a reference. The amount of picking and choosing required to end up with the claimed compounds of the present claims from the disclosure of Creswell without guidance toward compounds of the present claims is more than what is required in a proper case of obviousness. Creswell does not disclose any individual embodiment with sufficient specificity to lead one of ordinary skill in the art to the claimed invention. One of ordinary skill in the art should not have to pick and choose various groups in a reference's broad disclosure without motivation for such choices if said reference truly renders obvious a claimed invention.

The non-obviousness of the compounds of the claims is controlled by strong Federal Circuit precedent. Exemplary such Federal Circuit cases include *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) and *In re Baird*, 16 F.2d 380, 29 U.S.P.Q. 2d 1550 (Fed. Cir. 1994).

Baird's claimed compounds had the following structure:



wherein each of the two OH-groups was esterified with one of three dicarboxylic acids (succinic (4 carbon atoms), glutaric (5 carbon atoms) or adipic (6 carbon atoms).) The reference there had a very broad general formula encompassing, in very general terms, compounds possessing both components of Baird's claims, i.e., the above-pictured central diphenyl moiety (bisphenol A) and the terminal dicarboxylic acid esterifying groups. However, the general formula also disclosed the possibility of highly varied substitution on each of the phenyl rings, the possibility that the central three carbon atom propyl moiety to which each phenyl group is joined in the bisphenol A structure pictured above could instead also be a very wide variety of groups such as other alkylene groups, alkylidene groups or cycloalkylidene groups. Instead of the hydroxy groups at the terminal positions of bisphenol A, the phenyl rings in the reference could also be any of a large variety of possibilities, where between the O atom and the H atom of hydroxyl, there could be present $(RO)_x$ groups which were the same or different. The reference also specifically named, among twenty typical dicarboxylic acids for esterification, the three recited in Baird's claim.

The Court in *Baird* relied on the *Jones* holding quoted above, to quickly dismiss the Patent and Trademark Office's contention that the generally encompassing formula alone was sufficient to render Baird's claimed species obvious. The Patent and Trademark Office, however, "repeatedly emphasized[s]" that Baird's more specific disclosure disclosed "derivatives" of bisphenol A. The Court described these derivatives, showing that they differed from the above-pictured bisphenol A by containing between the O and H atoms in the terminal hydroxy groups, a variety of alkoxy moieties. The Court emphasized that by focusing on these preferred moieties, (derivatives of bisphenol A containing -O-ethyl, -O-

propyl, -O-isopropyl), Baird was teaching away from the selection of bisphenol A itself. By suggesting such derivatives, the reference "does not describe or suggest bisphenol A and therefore does not motivate the selection of bisphenol A." (*Baird*, 29 U.S.P.Q. 2d at 1552)

The Court concluded that given (a) the vast number of diphenols encompassed by the reference's general disclosure, and (b) that the mentioned diphenols more specifically disclosed by the reference as typical, preferred or optimum were different from *Baird's* bisphenol A structure, the reference did not suggest the selection of bisphenol A.

Analogously here, the specific compounds disclosed by Creswell in combination with the general formula of the reference amount to a teaching away from selections such that compounds of the present claims would be achieved. Nothing in Creswell's general disclosure suggests that compounds prepared therein should be modified as required to arrive at the claimed pyrazole, furan or thiphene urea compounds of formula I herein with the bridged cyclic group for "B," and especially not in combination with the right choices therein for X, one of (R_1, R_2 and/or R_3), HET and R_{11}, of these, where no preference is given to values for R_1, R_2 and R_3 or R_{11}. That they could be so modified does not establish obviousness. See *Jones*, above.

The rejections should be withdrawn based on structural non-obviousness alone. Nevertheless, applicants provide the following comments.

The Office Action alleges that the arguments previously submitted were not convincing on the basis that the references were attached individually. Applicants respectfully submit the references were not attacked individually, but rather their respective disclosed compounds were discussed as being dissimilar[1] such that one of ordinary skill in the art would not consider the use disclosed for one of these references to be relevant to the use of the compounds of the other. Why would one of ordinary skill in the art combine the teachings of two references when the compounds disclosed therein are very different structurally and are not shown to have a common mode of action while the disease identified in each reference include atherosclerosis?

Creswell teaches the compounds disclosed treat hypercholesteromelia and atherosclerosis by inhibiting the enzyme acyl-coenzyme A: cholesterol acyl transfurage to prevent the intestinal absorption of dietary cholesterol. Adams teaches the compounds

[1] The compounds of Creswell, i.e., of formula I therein disclosed on column 2, all contain a phenyl group connected via a urea group to a heterocyclic moiety. There is no corresponding urea group anywhere in the compounds of Adams, i.e., of formula I therein disclosed on column 3, which

disclosed treat a very large number of diseases, some of which are p38 mediated diseases, by inhibiting pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF (see, column 36, lines 57-60).

There is an indication the compounds of Adams will inhibit ACAT in treating atherosclerosis such that there is no hint or suggestion the compounds of Creswell will inhibit IL-1 or other pro-inflammatory cytokines so as to treat p38 mediated diseases.

Nothing in the art, including these references, teaches or suggests to one of ordinary skill in the art that the compounds taught by Creswell for atherosclerosis would be effective in treating inflammatory diseases such as rheumatoid arthritis. No criteria has been presented that any compound that has activity against atherosclerosis would have activity against rheumatoid arthritis.

The Examiner states that Adams is relied on to show that "both atherosclerosis and rheumatoid arthritis are known to be similarly treatable and are both known to be mediated by p38." (Emphasis added.) However, one of ordinary skill in the art looking at Adams has no basis to conclude or even suspect that all the diseases listed are "similarly treatable" by agents not shown or suggested by Adams.

Supplementally, whether both atherosclerosis and rheumatoid arthritis are taught or otherwise known to be a p38 mediated diseases is not relevant to the issue of obviousness when it comes to the specific issue of whether the compounds of formula I would be useful for the treatment of diseases identified as p38 diseases, inflammatory diseases or those specific diseases listed in claims 17 and 30. Such general information does not teach or suggest to one of ordinary skill in the art that the compounds of Creswell are actually effective in inhibiting p38 or in treating p38 mediated diseases generally or in treating inflammatory diseases generally. For example, such information does not exclude the possibility that other pathways may mediate atherosclerosis by the compounds of Creswell.

The Office Action in response to the immediately above line of arguments, made the following allegations:

> that the fact that the treatment of rheumatoid arthritis with the claimed compounds is rendered obvious by the prior art would be sufficient to meet the claims even without a teaching that atherosclerosis and/or rheumatoid arthritis are p38 mediated diseases because the discovery of a new pathway for the treatment of the same disease with the same compounds does not render the same treatment patentable.

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are tri-substituted imidazole compounds. There is absolutely no overlap between the two generic formulae, and no suggestion they are similar.

Applicants are not treating the same disease with the same compound as the prior art. Creswell teaches the treatment of diseases different than applicants with different compounds. Adams discloses the treatment of inflammatory diseases with compounds which are unrelated to those claimed by applicants and also very different than those taught by Creswell.

For all the foregoing reasons, the claims of the present application are not obvious over the combination of these references.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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